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Synthesis of Imidazole Derivatives Containing Biologically Active Units

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Abstract□Reaction of oxazolin-5-ones **1** with *p*-amino-diphenylamine was resulted in the formation of the corresponding imidazolin-5-ones **2** which on treatment with sulphur afforded phenothiazines **3**. Acridine derivatives **5** were obtained from acetylaminodiphenylamines derivatives **6** on heating with $ZnCl_2$ at 200 °C. **3** reacted with chloroacetyl chloride to give **7** which reacted in turn with different amines to give **8**. Antibacterial activity of the obtained products was studied.

Key words□Imidazolines, Phenothiazines, Acridines, Antibacterial Activity.

The discovery that phenothiazine[1], imidazoline[2] and acridine[3-5] derivatives possess high degree of antibacterial, as well as, antimalarial activity[6,7] has led to synthesis of a large number of additional substituted imidazolines with the objective of seeking derivatives with the widest antibacterial spectrum and optimum effectiveness against Gram positive and Gram negative organisms. It is the purpose of this paper to describe the new substituted imidazole derivatives which have been prepared in our laboratories.

Now, compounds **1a-e** reacted with *p*-aminodiphenylamine in acetic acid and in the presence of fused sodium acetate to give **2a-e**. Structures of the obtained products were established from its IR spectra which revealed the presence of absorption bands at 1710, 3350 cm^{-1} for cyclic CO and NH groups, respectively. ^{1}H-NMR spectrum of **2e** revealed signals at $\delta = 6.9$-7.8 ppm for aromatic and ylidene protons and at $\delta = 5.7$ ppm and 3.6 ppm for NH and OCH_3 groups, respectively.

2a-e could be readily cyclized to the corresponding phenothiazino-imidazoline derivatives **3a-e** on boiling in *o*-dichlorobenzene containing the equivalent quantity of sulphur flower. IR spectra of **3a-e** revealed the presence of C-S band at 750 cm^{-1}. Structure **3e** was established based on the presence of two less protons in the aromatic region in comparison with ^{1}H-NMR spectrum of **2e**. ^{1}H-NMR of **3a** revealed the presence of signals at $\delta = 7$-7.8 ppm (m, 17H, aromatic and ylidenic protons); 5.6 ppm (s, 1H, NH) and 3.6 ppm (s, 3H, OCH_3). Oxidation of **3a-e** with H_2O_2 afforded the corresponding sulphones **4a-e**. Structure **4** was established from IR spectra of the obtained products which indicated an absorption bands at 1350, 1160 cm^{-1} for assym. and sym. SO_2 and also a broad band for NH group at 3250-3100 cm^{-1}.

Attempted preparation of acridine derivatives **5** *via* acetylation of **2a-e** in different solvents and in the presence of anhydrous $ZnCl_2$ was found unsuccessful and in each case the reaction was resulted in the formation of acetyl derivatives **6a-e**. ^{1}H-NMR of **6c** exhibited signals at 7.7-6.8 ppm (m, 19H, aromatic and ylidenic protons) and at 2.1 ppm (s, 3H, $COCH_3$). Compounds **5a-e** were obtained in this work, by heating **6a-e** at 200 °C without solvent in the presence of anhydrous $ZnCl_2$ and a remarkable change in colour was observed followed by formation of reddish brown products while heating which gave analytical data compatible with the acridine derivatives **5a-e**. The above results for preparation of **5** was in complete agreement with that previously observed by Hamer[8]. IR spectra of **5** revealed the absence of absorption band for carbonyl group. ^{1}H-NMR spectra of **5c** showed signals at $\delta = 7.8$-6.9 ppm (m, 17H, aromatic and ylidenic protons) and at $\delta = 2.2$ ppm (s, 3H, CH_3).

Acridine derivatives **5a-e** could be also obtained by direct condensation of **1a-e** with 2-amino-9-me-

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thyl-acridine.

Also, chloroacetylation of **3b** and **3d,e** furnished the expected N-chloroacetylphenothiazine derivatives **7a-c** which in turn reacted with methylamine and diethylamino-propylamine to give the corresponding compounds **8a-f**, respectively.

IR spectrum of **7a** showed absorption bands at 1710 cm^{-1} for cyclic CO group and 1680 cm^{-1} for exocyclic CO group. ^{1}H-NMR spectrum of **7c** showed signals at $\delta = 7.0$-7.8 ppm (m, 17H, aromatic and ylidenic protons), at $\delta = 3.2$ ppm (s, 2H, CH_2) and at 3.8 ppm (s, 3H, OCH_3). Structure **8** was established from IR spectrum which revealed an additional absorption band at 3300 cm^{-1} for NH group and also from ^{1}H-NMR spectrum of **8c** which showed signals at $\delta = 7.9$-6.8 ppm (m, 17H, aromatic and ylidenic protons) and at δ 3.3 ppm (s, 2H, CH_2); 3.6 (s, 3H, CH_3) and at 3.8 ppm (s, 3H, OCH_3).

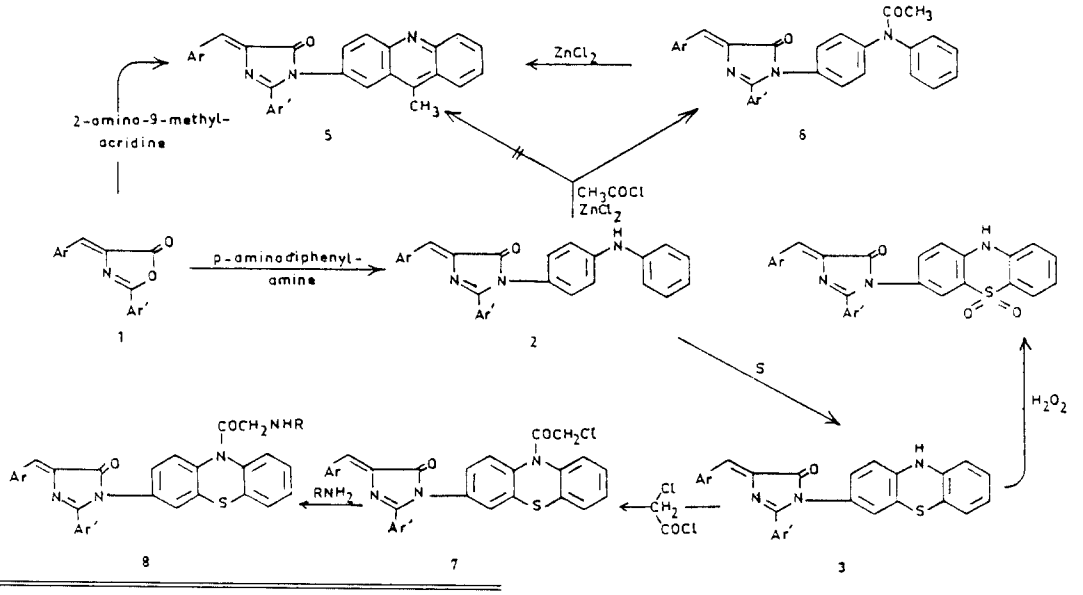
BACTERIOLOGICAL TESTING AND RESULTS

Five bacterial cultures were selected at random for initial screening included both Gram-positive and Gram-negative bacteria of several genera having different nutritional requirements and metabolic activities. Several new compounds were tested *in vitro* at concentration of 100 μg/ml. Data pertaining to the relation between structures and bacterial activity of the newly synthesized compounds are presented in Table I. It is to be noted first that compounds listed here have activity *vs Bacillus subtilis*. It has been found that introduction of chloroacetyl group in **3** (compounds **7a-c**) completly abolishes the activity and the most active compounds are acetylaminoalkyl derivatives (**8a-f**).

Table I. Antibacterial activities of compounds 3-8

Compound in conc. 100 μg/ml	Inhibition zone [cm^2]				
	Bacillus subtilis	*Staphylococcus aureus*	*Sarcina lutea*	*Escherichia coli*	*Candida albicans*
3a	++	+	−	+	−
b	++	−	+	−	−
c	−	−	+	−	−
d	++	+	+	+	−
4a	+	−	−	−	−
b	−	+	+	−	+
c	++	+	−	−	−
d	++	+	−	+	−
e	+++	++	++	−	−
5a	+	−	−	++	+
b	++	+	+	−	−
c	+++	++	++	−	−
6a	+	+	+	−	+
b	−	−	+	+	−
7a	−	+	−	−	−
b	−	−	−	−	−
c	+	−	+	+	−
8a	+++	++	−	+	+
b	++	++	+	−	−
c	++	++	++	+	+
d	+++	+	+	++	+
e	+++	+	+++	−	+
f	+++	+	++	−	++

− < 1 cm, + 1-1.5 cm, ++ 1.5-2 cm; +++ > 2 cm.



2-6	Ar	Ar'
a	$C_6H_4{\cdot}CH_3$-p	$C_6H_4{\cdot}OCH_3$-p
b	$C_6H_4{\cdot}OCH_3$-p	$C_6H_4{\cdot}OCH_3$-p
c	C_6H_4-Cl-p	C_6H_5
d	$C_6H_4{\cdot}N(CH_3)_2$-p	C_6H_5
e	$C_6H_4{\cdot}OCH_3$-p	C_6H_5

7	Ar	Ar'
a	$C_6H_4{\cdot}OCH_3$-p	$C_6H_4{\cdot}OCH_3$-p
b	$C_6H_4{\cdot}N(CH_3)_2$-p	C_6H_5
c	$C_6H_4{\cdot}OCH_3$-p	C_6H_5

8	Ar	Ar'	R
a	$C_6H_4{\cdot}OCH_3$-p	$C_6H_4{\cdot}OCH_3$-p	$-CH_3$
b	$C_6H_4{\cdot}OCH_3$-p	$C_6H_4{\cdot}OCH_3$-p	$-(CH_2)_3N(C_2H_5)_2$
c	$C_6H_4{\cdot}N(CH_3)_2$-p	C_6H_5	$-CH_3$
d	$C_6H_4{\cdot}N(CH_3)_2$-p	C_6H_5	$-(CH_2)_3N(C_2H_5)_2$
e	$C_6H_4{\cdot}OCH_3$-p	C_6H_5	$-CH_3$
f	$C_6H_4{\cdot}OCH_3$-p	C_6H_5	$-(CH_2)_3N(C_2H_5)_2$

Also, conversion of acetyl derivatives **6** to acridines **5** gives products which are devoid of interest as antibacterial agents. Most of the tested compounds were found inactive *vs Escherichia coli* and *Candida albicans*.

EXPERIMENTAL METHODS

Melting points are uncorrected. Infrared spectra were recorded using a Pye Unicam SP-1000 spectrophotometer. The ^{1}H-NMR spectra were measured on a Varian EM-390 90MHz using TMS as an internal standard and chemical shifts are expressed as δ ppm. Analytical data were obtained from the analytical Data Unit at Cairo University.

***Syntheses of* Δ^2*-imidazolin-5-ones* (2a-e):**

A mixture of oxazolone **1** (0.01 mol), *p*-aminodiphenylamine (0.01 mol) and fused sodium acetate (0.2 gm) in acetic acid (50 m*l*) was heated under reflux for 3 h. The solid product, so formed, on cooling was collected by filtration, then crystallized and identified as **2a-e** (cf. Table II).

***Syntheses of phenothiazino-imidazolines* (3a-e):**

2(0.01 mol), sulphur flower (0.02 mol) and iodine (0.1 g) in *o*-dichlorobenzene (30 m*l*) was heated at 200-210 °C for 2 h. The reaction mixture was triturated with pet. ether (40-60 °C) to give a product which recrystallized and identified as **3** (cf. Table II).

***Oxidation of* 3 *to sulfones* (4a-e):**

A mixture of **3**(0.01 mol) and H_2O_2 (30%; 20 m*l*) in glacial acetic acid (20 m*l*) was heated under reflux for 10 h. The reaction mixture was diluted with ice-cold water and the product, so formed, was recrystallized and identified as **4** (cf. Table II).

Table II. Physical data of compounds 3-8

Compd.	M.p. (°C)	Yield (%) (Cryst. solvent)*	Mol. formula (Mol. Mass)**
2a	226	85 (Ac)	$C_{30}H_{25}N_3O_2$ (459.3)
2b	234	86 (Ac)	$C_{30}H_{25}N_3O_3$ (475.3)
2c	224	82 (Ac)	$C_{28}H_{20}N_3OCl$ (449.75)
2d	242	81 (Ac)	$C_{30}H_{26}N_4O$ (458.33)
2e	246	75 (Ac)	$C_{29}H_{23}N_3O_2$ (445.3)
3a	218	78 (B)	$C_{30}H_{23}N_3O_2S$ (489.36)
3b	204	80 (B)	$C_{30}H_{23}N_3O_3S$ (505.36)
3c	182	74 (B)	$C_{28}H_{18}N_3OSCl$ (479.81)
3d	194	73 (B)	$C_{30}H_{24}N_4OS$ (488.39)
3e	198	85 (B)	$C_{29}H_{21}N_3O_2S$ (475.36)
4a	163	73 (B)	$C_{30}H_{23}N_3O_4S$ (521.36)
4b	152	75 (B)	$C_{30}H_{23}N_3O_5S$ (537.36)
4c	212	62 (B)	$C_{28}H_{18}N_3O_3SCl$ (511.8)
4d	203	73 (B)	$C_{30}H_{24}N_4O_3S$ (520.39)
4e	181	70 (B)	$C_{29}H_{21}N_3O_4S$ (507.36)
5a	213	75 (Ac)	$C_{32}H_{25}N_3O_2$ (483.3)
5b	260	72 (Ac)	$C_{32}H_{25}N_3O_3$ (499.3)
5c	296	65 (Ac)	$C_{30}H_{20}N_3OCl$ (473.77)
5d	>300	78 (Ac)	$C_{32}H_{26}N_4O$ (482.35)
5e	284	70 (Ac)	$C_{31}H_{23}N_3O_2$ (469.3)
6a	150	77 (E)	$C_{32}H_{27}N_3O_3$ (501.3)
6b	144	70 (E)	$C_{32}H_{27}N_3O_4$ (517.3)
6c	196	72 (Ac)	$C_{30}H_{22}N_3O_2Cl$ (491.77)
6d	230	81 (Ac)	$C_{32}H_{28}N_4O_2$ (500.35)
6e	200	80 (Ac)	$C_{31}H_{25}N_3O_3$ (487.3)
7a	245	72 (T)	$C_{32}H_{24}N_3O_4SCl$ (582.08)
7b	283	75 (T)	$C_{32}H_{25}N_4O_2SCl$ (565.09)
7c	252	65 (T)	$C_{31}H_{22}N_3O_3SCl$ (552.02)
8a	195	53 (E)	$C_{33}H_{28}N_4O_4S$ (576.65)
8b	210	64 (E)	$C_{39}H_{41}N_5O_4S$ (675.80)
8c	241	70 (E)	$C_{33}H_{29}N_5O_2S$ (559.66)
8d	236	72 (E)	$C_{39}H_{42}N_6O_2S$ (658.83)
8e	201	78 (A)	$C_{32}H_{26}N_4O_3S$ (546.62)
8f	169	73 (E)	$C_{38}H_{39}N_5O_3S$ (645.79)

*) Ac = Acetic acid, E = Ethanol, B = Benzene, T = Toluene

**) Satisfactory microanalysis: C ± 0.47; H ± 0.47; N ± 0.20.

Reaction of **2** *with acetyl chloride: Formation of* **6a-e**:

A mixture of **2** (0.01 mol), acetyl chloride (0.015 mol) and anhydrous $ZnCl_2$ was heated for 1 h in dry conditions. Excess acetyl chloride was then evaporated in vacuo and the remaining product was triturated with water. The solid product, so formed, was collected by filtration and crystallized from the appropriate solvent to give **6**. (cf. Table II).

Preparation of acridino-imidazolines **5a-e**:

a) From oxazolines (1) and 2-amino-9-methylacridine

A mixture of oxazoline **1** (0.01 mol), 2-amino-9-methylacridine (0.01 mol) and fused sodium acetate (0.2 gm) in acetic acid (50 m*l*) was heated for 3 h. The solid product, so formed, on cooling was collected by filtration, then recrystallized and identified as **5** (cf. Table II).

From imidazoline derivatives (6) and anhydrous $ZnCl_2$

A mixture of **6** (0.01 mol) and anhydrous $ZnCl_2$ was heated at 200 °C for 3 h. The product obtained was triturated for several times with water. The

solid product, so formed, was filtered off and identified (m.p., mixed m.p. and IR) as **5**.

Chloroacetylation of phenothiazines **(3a-e):**

To a solution of **3** (0.01 mol) in dry toluene (30 m*l*), chloroacetyl chloride (0.015 mol) was added and the reaction mixture was refluxed for 2 h, then evaporated in vacuo.

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